



CONFIDENTIAL

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Laboratoires Laphal
DRD
B.P. 7
13718 Allauch CEDEX
France

TEST SUBSTANCE
PADINOL SOLIDE

STUDY TITLE
ACUTE ORAL TOXICITY
IN RATS

STUDY DIRECTOR
Xavier Manciaux

STUDY COMPLETION DATE
5 May 1999

PERFORMING LABORATORY
CIT
Centre International de Toxicologie
BP 563 - 27005 Evreux - France

LABORATORY STUDY NUMBER
18360 TAR

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STATEMENT OF THE STUDY DIRECTOR

The study was performed in compliance with the principles of Good Laboratory Practice as described in:

- . OECD Principles on Good Laboratory Practice (as revised in 1997), ENV/MC/CHEM (98) 17.
- . Council Directive 87/18/EEC of 18 December 1986 on the harmonization of laws, regulations or administrative provisions relating to the application of the Principles of Good Laboratory Practice and the verification of their applications for tests on chemical substances (OJ No. L 15 of 17.1.87).
- . Instruction du 31 mai 1983 relative aux Bonnes Pratiques de Laboratoire dans le domaine de la Toxicologie Expérimentale (Ministère des Affaires Sociales et de la Solidarité Nationale).
- . US Food and Drug Administration, Good Laboratory Practice Regulations 21 CFR Part 58, December 22, 1978 (and subsequent amendments).

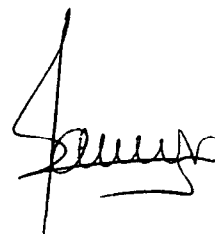
The study was also conducted in compliance with Animal Health regulation, in particular:

- . Council Directive 86/609/EEC of 24th November 1986 on the harmonization of laws, regulations or administrative provisions relating to the protection of animals used for experimental or other scientific purposes.

I declare that this report constitutes a true and faithful record of the procedures undertaken and the results obtained during the performance of the study.

This study was performed at CIT, Centre International de Toxicologie, BP 563, 27005 Evreux, France.

Toxicology



X. Manciaux
Study Director
Doctor of Pharmacy

Date: 5 May 1999

OTHER SCIENTISTS INVOLVED IN THIS STUDY

For Pharmacy: P.O. Guillaumat
Doctor of Pharmacy

For Toxicology: C. Pelcot
Study Supervisor

STATEMENT OF QUALITY ASSURANCE UNIT

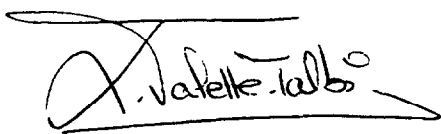
Type of inspections	Dates		
	Inspections	Reported to Study Director (*)	Reported to Management (*)
Protocol	22 February 1999	22 February 1999	22 February 1999
Study	18 March 1999	22 March 1999	22 March 1999
Report	28 April 1999	28 April 1999	4 May 1999

At about the same time as the study described in this report, "process-based" and routine facility inspections of critical procedures relevant to this study type were made by the Quality Assurance Unit.

The findings of these inspections were reported to the Study Director and to CIT Management.

The inspections were performed in compliance with CIT Quality Assurance Unit procedures and the Good Laboratory Practice.

The reported methods and procedures were found to describe those used and the results to constitute an accurate and complete reflection of the study raw data.



L. Valette-Talbi Date: 5 May 1999
Doctor of Biochemistry
Head of Quality Assurance Unit
and Scientific Archives

(*) The dates indicated correspond to the dates of signature of audit reports by Study Director and Management.

SUMMARY

At the request of Laboratoires Laphal, Allauch, France, the acute oral toxicity of the test substance PADINOL SOLIDE was evaluated in rats.

The study was conducted in compliance with the principles of Good Laboratory Practice Regulations.

Methods

The test substance was administered by oral route (gavage) to one group of five male and five female fasted Sprague-Dawley rats.

The test substance was prepared in 0.5% methylcellulose and administered to the animals at the dose of 2000 mg/kg, under a volume of 10 ml/kg.

One control group of ten animals (five males and five females) received the vehicle alone, under the same experimental conditions.

Clinical signs, mortality and body weight gain were checked for a period of up to 14 days following the single administration of the test substance.

All animals were subjected to necropsy.

Results

No clinical signs and no death were recorded during the study.

The body weight gain of the treated animals was similar to that of control animals.

No apparent abnormalities were observed at necropsy in all animals.

Conclusion

Under our experimental conditions, the oral LD₅₀ of the test substance PADINOL SOLIDE is higher than 2000 mg/kg in rats. No signs of toxicity were observed at this dose.

1. INTRODUCTION

The objective of this study was to evaluate the toxicity of the test substance PADINOL SOLIDE following a single oral administration in rats.

In the assessment of the toxic characteristics of a test substance, determination of acute oral toxicity is an initial step. It provides information on health hazards likely to arise following a short-term exposure by the oral route in Man.

The study was conducted in compliance with EEC recommendation No. 87/176/EEC, appendix I, adopted on 9th February 1987, published in JOCE on 16th March 1987, No. L73.

2. MATERIALS AND METHODS

2.1 TEST SUBSTANCE

2.1.1 Identification

The test substance PADINOL SOLIDE used in the study was supplied by Laboratoires Laphal.

The test substance was identified as follows:

- . name:
 - protocol and labelling: PADINOL SOLIDE
- . batch number:
 - protocol and labelling: PZH1326
- . description: white powder
- . quantity and container: 1 kg in one opaque plastic flask
- . date of receipt: 27 January 1999
- . storage conditions: at room temperature and protected from light.

Data relating to the characterization of the test substance are documented in a test substance data sheet and an analytical certificate (presented in appendix 1) provided by the Sponsor.

2.1.2 Vehicle

The vehicle used was 0.5% methylcellulose: methylcellulose, batch No. 15H0241 (Sigma, 38297 Saint-Quentin-Fallavier, France) and purified water (prepared at CIT by reverse osmosis).

2.1.3 Formulation procedure

On the day of treatment, the test substance was ground to a fine powder using a mortar and pestle, then was prepared at the chosen concentration in the vehicle.

2.2 TEST SYSTEM

2.2.1 Animals

Species, strain: rat, Sprague-Dawley ICO: OFA-SD (IOPS Caw).

Reason for this choice: rodent species generally accepted by regulatory authorities for this type of study.

Breeder: Iffa Crédo, 69210 L'Arbresle, France.

Number and sex: two groups of five males and five females each were used.

Age/weight: on the day of treatment, the animals were approximately 6 weeks old, and had a mean body weight \pm standard deviation of 187 ± 6 g for the males and 153 ± 6 g for the females.

Acclimatization: at least 5 days before the beginning of the study.

Identification of the animals: the animals were identified individually by earmarks or earnotches.

2.2.2 Environmental conditions

During the acclimatization period and throughout the study, the conditions in the animal room were set as follows:

- . temperature: $21 \pm 2^\circ\text{C}$

- . relative humidity: 30 to 70%

- . light/dark cycle: 12 h/12 h

- . ventilation: approximately 12 cycles/hour of filtered, non-recycled air.

The temperature and relative humidity were under continuous control and recording. The records were checked daily and filed. In addition to these daily checks, the housing conditions and corresponding instrumentation and equipment are verified and calibrated at regular intervals.

The animals were housed in polycarbonate cages (48 cm x 27 cm x 20 cm). Each cage contained one to seven animals of the same sex during the acclimatization period and five rats of the same sex during the treatment period. Each cage contained dust-free sawdust (SICSA, 94142 Alfortville, France).

Bacteriological and chemical analyses of the sawdust, including the detection of possible contaminants (pesticides, heavy metals), are performed regularly by external laboratories.

The results of these analyses are archived at CIT.

2.2.3 Food and water

All the animals had free access to A04 C pelleted diet (UAR, 91360 Villemoisson-sur-Orge, France), except as noted in "2.3.1 Fasting of the animals".

Each batch of food was analysed by the supplier for composition and contaminant levels.

The diet formula is presented in appendix 2.

Drinking water filtered by a FG Millipore membrane (0.22 micron) was provided *ad libitum*.

Bacteriological and chemical analyses of the water and diet, including the detection of possible contaminants (pesticides, heavy metals and nitrosamines), are performed regularly by external laboratories.

The results of these analyses are archived at CIT.

No contaminants were known to have been present in the diet, drinking water or bedding material at levels which may be expected to have interfered with or prejudiced the outcome of the study.

2.3 TREATMENT

2.3.1 Fasting of the animals

The animals were fasted for an overnight period of approximately 18 hours before dosing, but had free access to water.

Food was given back approximately 4 hours after administration of the test substance.

2.3.2 Study design

The test substance was prepared in the vehicle. It was administered to a group of ten animals (five males and five females) at the dose of 2000 mg/kg, under a volume of 10 ml/kg.

One control group of ten animals (five males and five females) received the vehicle alone under the same experimental conditions.

The administration was performed in a single dose by oral route using a metal gavage tube fitted to a 5 ml glass syringe (0.05 ml graduations).

The volume administered to each animal was adjusted according to body weight determined on the day of treatment.

2.3.3 Chronology of the study

The single administration was performed on 18 March 1999 in the morning (day 1) and was followed by a 14-day observation period until 1 April 1999 (day 15).

2.4 CLINICAL EXAMINATIONS

2.4.1 Clinical signs and mortality

The animals were observed frequently during the hours following administration of the test substance, for detection of possible treatment-related clinical signs. Thereafter, observation of the animals was made at least once a day until day 15.

Type, time of onset and duration of clinical signs were recorded for each animal individually.

Time of death was recorded individually, in terms of the number of hours or days after dosing.

2.4.2 Body weight

The animals were weighed individually just before administration of the test substance on day 1 and then on days 5, 8 and 15.

2.5 NECROPSY

On day 15, all animals were killed by carbon dioxide asphyxiation and a macroscopic examination was performed.

After opening the thoracic and abdominal cavities, a macroscopic examination of the main organs (digestive tract, heart, kidneys, liver, lungs, pancreas, spleen and any other organs with obvious abnormalities) was performed.

In case of macroscopic lesions, organ samples were taken and preserved in 10% buffered formalin.

No microscopic examination was performed.

2.6 DATA EVALUATION

Evaluation of the toxicity of the test substance following a single oral administration in rats should include the relationship, if any, between the animals' exposure to the test substance and the incidence and severity of all abnormalities including behavioural and clinical abnormalities, macroscopic lesions, body weight changes, mortality and any other toxic effects.

2.7 PROTOCOL ADHERENCE

The study was performed in accordance with the Study Protocol No. 18360 TAR and subsequent amendments. There were no deviations from the agreed Study Protocol.

2.8 ARCHIVING

The study documentation and specimens generated during the course of the study are archived at CIT, 27005 Evreux, France, for 5 years after the end of the *in vivo* phase of the study.

The archived study materials include:

- . protocol and possible amendments,
- . raw data,
- . correspondence,
- . final report and possible amendments.

On completion of this period, the archived study materials will be returned to the Sponsor, or may be archived at CIT for a further period.

3. RESULTS

3.1 CLINICAL EXAMINATIONS

3.1.1 Clinical signs and mortality (table 1)

No death occurred during the observation period.

No clinical signs were observed during the study.

3.1.2 Body weight (figures 1 and 2, table 2)

The body weight gain of the treated animals was similar to that of control animals.

3.2 PATHOLOGY (table 3)

Macroscopic examination of the main organs of the animals revealed no apparent abnormalities.

4. CONCLUSION

Under our experimental conditions, the oral LD₅₀ of the test substance PADINOL SOLIDE is higher than 2000 mg/kg in rats. No signs of toxicity were observed at this dose.

Figure 1: Body weight of males

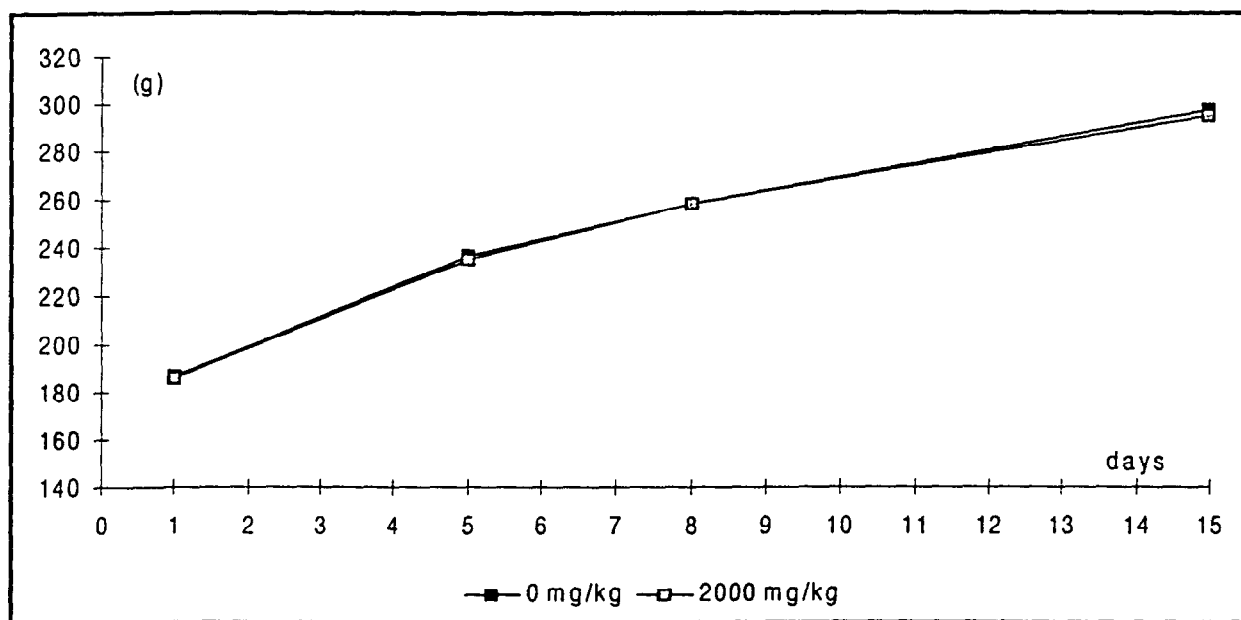


Figure 2: Body weight of females

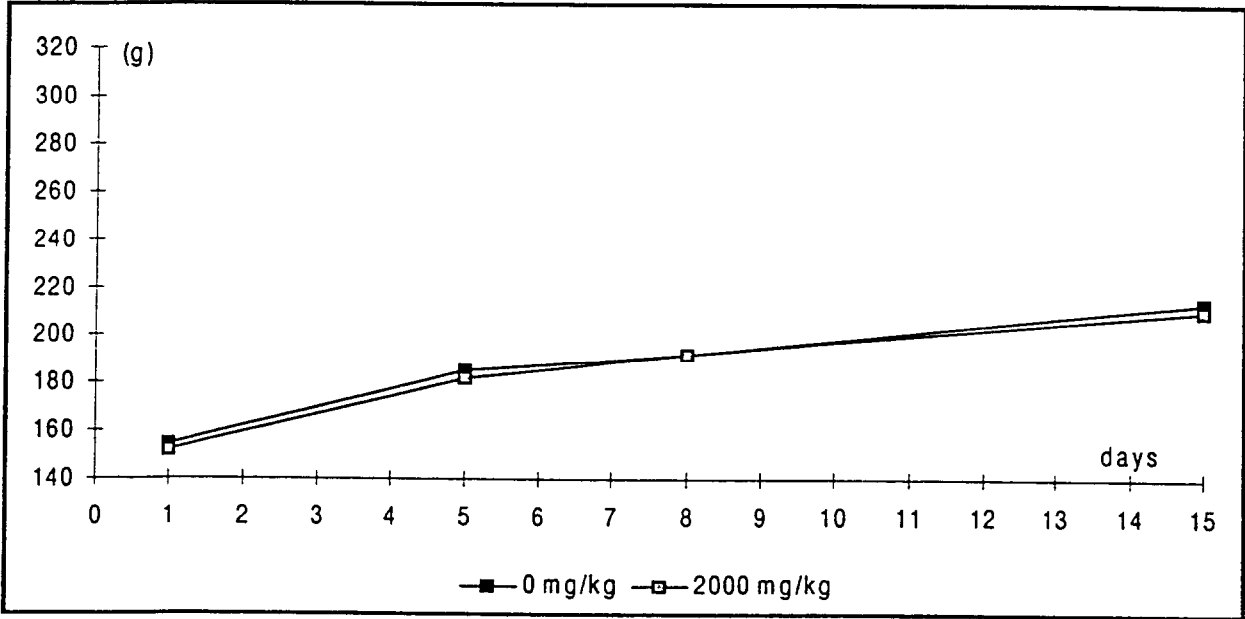


Table 1: Individual clinical signs and mortality

Dose (mg/kg)	Time	Animals		Mortality	Clinical signs
		Males	Females		
0	30 min	01-02-03-04-05	06-07-08-09-10	No	None
	1h - 2h - 4h				
	D 2 to D 15				
2000	30 min	11-12-13-14-15	16-17-18-19-20	No	None
	1h - 2h - 4h				
	D 2 to D 15				

min : minutes

h : hour

D : day

Table 2: Individual and mean body weight and weekly body weight change (g)

Dose mg/kg	Volume ml/kg	Sex	Animals	Days						
				1	(1)	5	(1)	8	(1)	15
0	10	Male	01	190	50	240	19	259	40	299
			02	183	48	231	16	247	36	283
			03	182	56	238	28	266	44	310
			04	183	40	223	18	241	42	283
			05	196	55	251	27	278	33	311
			M	187	50	237	22	258	39	297
			SD	6	6	10	6	15	4	14
			06	158	27	185	7	192	20	212
			07	154	30	184	6	190	32	222
0	10	Female	08	152	27	179	17	196	15	211
			09	151	32	183	-3	180	17	197
			10	156	38	194	8	202	23	225
			M	154	31	185	7	192	21	213
			SD	3	5	6	7	8	7	11
2000	10	Male	11	185	51	236	24	260	46	306
			12	184	51	235	19	254	36	290
			13	192	48	240	25	265	36	301
			14	192	49	241	23	264	33	297
			15	178	47	225	22	247	33	280
			M	186	49	235	23	258	37	295
			SD	6	2	6	2	8	5	10
			16	146	27	173	8	181	12	193
			17	157	31	188	9	197	21	218
2000	10	Female	18	161	31	192	16	208	25	233
			19	151	35	186	10	196	20	216
			20	142	27	169	6	175	13	188
			M	151	30	182	10	191	18	210
			SD	8	3	10	4	13	6	19

(1) - Body weight gain
M - Mean
SD - Standard Deviation

Table 3: Individual macroscopic examinations at necropsy

Dose mg/kg	Time	Animals		Macroscopic abnormalities
		Males	Females	
0	D 15	01-02-03-04-05	06-07-08-09-10	No apparent abnormalities
2000	D 15	11-12-13-14-15	16-17-18-19-20	No apparent abnormalities

D: day

APPENDICES

1. Test substance data sheet and analytical certificate



FICHE DE RENSEIGNEMENTS SUR LE PRODUIT A TESTER
TOXICOLOGIE COURT-TERME - ECOTOXICOLOGIE - TOXICOLOGIE GENETIQUE

TEST SUBSTANCE DATA SHEET
SHORT-TERM TOXICOLOGY - ECOTOXICOLOGY - GENETIC TOXICOLOGY

Nom du demandeur Sponsor: Laboratoires LAPHAL

Produit/Test substance: PADINOL solide

N° de lot/Batch No.: PZH-1326

Conditions de stockage/Storage conditions: A l'abri de la lumière et à température ambiante

En l'absence d'information, stockage dès réception à température ambiante sans précautions particulières/*In the absence of information the test substance will be stored at room temperature without any specific precautions.*

Stabilité du produit dans les conditions de stockage/*Stability of the test substance under the storage conditions:*

- stable au moins 6 mois/*stable at least 6 months*

☒ Oui/Yes

☐ Non/No

- si la stabilité est inférieure à 6 mois, préciser la durée de stabilité/*if the test substance is not stable for 6 months, indicate the duration of stability:*

Devenir du produit/*Fate of the test substance*: renvoi au demandeur/*return to the Sponsor*:

☒ Oui/Yes (en port dû)/*at the client expense*: adresse/*address*

☐ Non/No: procédé de destruction/*destruction procedure*

En l'absence d'information, le produit sera détruit 12 mois après la remise du rapport final/*If no information is supplied, the test substance will be destroyed 12 months following finalisation of the report.*

Caractéristiques physiques/*Physical properties*

Pureté/*Purity*: ✓

Aspect/*Appearance*: Poudre microcristalline / ~ 50 µm

Couleur/*Colour*: blanc à blanc cassé

Solubilité dans l'eau (mg/l)/*Solubility in water (mg/l)*: insoluble mais dispersible

Poids moléculaire/*Molecular weight*: ✓

pH: ✓

Densité/*Specific gravity*: 0,33

Ecotoxicologie/*Ecotoxicology*

Pression de vapeur (atm)/*Vapour pressure (atm)*: ✓

Stabilité dans l'eau/*Stability in water*: ✓

Photodégradabilité/*photodegradability*: ✓

Biodégradabilité/*Biodegradability*: ✓

Coefficient de partage Octanol/Eau/*Log K_{ow}*: ✓

Si le produit est peu soluble dans l'eau, sélectionner le véhicule à utiliser de préférence/*For a product with low solubility in water, state preferred vehicle*

Toxicité aiguë ou Toxicité génétique (in vivo)/*Acute toxicology or Genetic Toxicology (in vivo)*

NaCl (0.9%)

carboxyméthylcellulose (0.5%)

PEG 300

méthylcellulose (0.5%)

huile de germe de maïs/*corn oil*

autre (préciser)/*other (state preference)*:

Ecotoxicologie ou Toxicité génétique (in vivo)/*Ecotoxicology or Genetic Toxicology (in vitro)*

acetone

acetonitrile

ethanol

dimethylsulphoxide

tetrahydrofuran

tertio butanol/*tertiary butanol*:

methanol

dimethyl formamide

autre (préciser)/*other (state preference)*:

Préparation du produit dans le véhicule/*Preparation of the test substance in the auxiliary substance*: ✓

(ultrasons/*ultrasonics*; chauffage/*heating*...)

Précautions d'emploi/*Precautions for use*: ✓

Incompatibilité avec le verre ou les matières plastiques/*Possible incompatibility with glass or plastic*: ✓

Mesures à prendre en cas de contamination/*Precautions to take in case of contamination*: ✓

Signature du mandant/*Sponsor's signature*:

JC Voinin

Date:

17/02/99

Laboratoires TEXINFINE

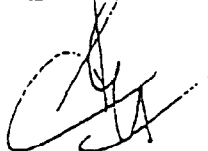
PADINOL SOLIDE	BULLETIN D'ANALYSES	LOT : PZH1326 date : 11/01/1999
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Caractères organoleptiques	Couleur : blanc à blanc cassé Odeur : caractéristique Aspect : poudre microcristalline $\varnothing \sim 50\mu\text{m}$
Titre	50 000 U.I.Kg ⁻¹
Quantité	1 Kg
Emballage	Flacon plastique blanc
Nombre	1 flacon
Solubilité	Eau : insoluble mais dispersible Solvants organiques acides: insoluble Solutions alcalines diluées: partiellement soluble et gonflement des particules. Solutions acides diluées: insoluble
Densité	0.33
Spectrophotométrie UV-VIS	204nm - 240nm -
Chromatographie sur couche mince (procédure TEXACLV0898-3)	présence des stérols conforme Rf:0.4
Analyse microbiologique	Conforme
3-hydroxy stérols (procédure TEXACLV0898-4)	2.5mg.Kg ⁻¹
Activité	Conforme : supérieur au témoin II.-I

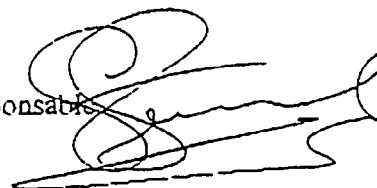
Conditions de stockage : A l'abri de la lumière et à température ambiante

Stabilité : 2 ans à date d'analyses

Le technicien



Le responsable



2. Diet formula

Ref: A04

COMPLETE DIET**RAT AND MOUSE MAINTENANCE DIET**

Appearance: 15 mm diameter pellets or powder

Conditioning: 25 kg double paper bag with aluminium on the outside

Daily portion: Rat 18-25 g, Mouse 5-10 g, water *ad libitum*.**FORMULA %**

Cereals and cereal byproducts.....	88
Vegetable protein (soya bean meal, yeast)	7
Animal protein (fish).....	2
Vitamin and mineral mixture.....	3

AVERAGE ANALYSIS %

Calorific value (KCal/kg)	2900
Moisture	12
Proteins	17
Lipids	3
Carbohydrates (N.F.E.)	58.7
Fibre	4
Minerals (ash)	5

MINERALS (calculated in mg/kg)

	Nat val.	CMV val.	Total
P	5900	0	5900
Ca	3300	5000	8300
K.....	6700	0	6700
Na.....	300	1600	1900
Mg.....	1900	100	2000
Mn.....	50	40	90
Fe.....	90	150	240
Cu.....	15	15	30
Zn.....	40	45	85
Co.....	T	1.5	1.5
I.....	0.3	0	0.3

AMINO ACID VALUES
(calculated in mg/kg)

Arginine	9800
Cystine	2300
Lysine.....	8500
Methionine.....	3200
Tryptophan.....	1900
Glycine.....	8100

FATTY ACID VALUES
(calculated in mg/kg)

Palmitic acid	2600
Palmitoleic acid.....	Traces
Stearic acid.....	500
Oleic acid	8000
Linoleic acid.....	14500
Linolenic acid.....	Traces

VITAMINS (calculated per kg)

	Nat val.	CMV val.	Total
Vitamin A	Traces	7500 IU	7500 IU
Vitamin D3	Traces	1500 IU	1500 IU
Vitamin B1	6 mg	1 mg	7 mg
Vitamin B2	2 mg	4.5 mg	6.5 mg
Vitamin B3	10 mg	6.5 mg	16.5 mg
Vitamin B6	1.3 mg	1.3 mg	2.6 mg
Vitamin B12	0.01 mg	0.01 mg	0.02 mg
Vitamin E	15 mg	15 mg	30 mg
Vitamin K3	0.25 mg	2.25 mg	2.5 mg
Vitamin PP	60 mg	15 mg	75 mg
Folic acid	0.5 mg	0 mg	0.5 mg
Biotin	0.04 mg	0 mg	0.04 mg
Choline	1200 mg	400 mg	1600 mg

Available under quality "Control Ref.: A04 C "

3. Protocol



Evreux, 23 February 1999

PADINOL SOLIDE
ACUTE ORAL TOXICITY
IN RATS

Protocol from : CIT
Centre International de Toxicologie
BP 563 - 27005 Evreux CEDEX
France

Sponsor : Laboratoires Laphal

Address : DRD
B.P. 7
13718 Allauch CEDEX
France

Study Monitor : J.C. Voirin

Study Director : X. Manciaux

Study Number : 18360 TAR

1. INTRODUCTION

1.1 Objective

The objective of this study is to evaluate the potential toxicity of the test substance after a single administration by oral route in rats.

1.2 Regulatory compliance

This protocol complies with the EEC recommendation No. 87/176/EEC, appendix I, adopted on 9th February 1987, published in JOCE on 16th March 1987, No. L73.

The study will be conducted in compliance with Good Laboratory Practice Regulations:

- . Council Directive 87/18/EEC of 18 December 1986 on the harmonization of laws, regulations or administrative provisions relating to the application of the Principles of Good Laboratory Practice and the verification of their applications for tests on chemical substances (OJ No. L 15 of 17.1.87).
- . Instruction du 31 mai 1983 relative aux Bonnes Pratiques de Laboratoire dans le domaine de la Toxicologie Expérimentale (Ministère des Affaires Sociales et de la Solidarité Nationale).
- . US Food and Drug Administration, Good Laboratory Practice Regulations 21 CFR Part 58, December 22, 1978 (and subsequent amendments).
- . OECD principles of Good Laboratory Practice (as revised in 1997), ENV/MC/CHM (98) 17.

This study will be conducted in compliance with the Animal Health regulation, in particular:

- . Council Directive 86/609/EEC of 24 November 1986 on the harmonization of laws, regulations or administrative provisions relating to the protection of animals used for experimental or other scientific purposes.

2. TEST SUBSTANCE AND VEHICLE

2.1 Identification

2.1.1 Test substance

. **Denomination:** PADINOL SOLIDE

. **Batch No.:** PZH1326

. **Description:** white powder

. **Storage conditions:** at room temperature and protected from light

Purity, composition and stability of the batch, as well as any specific handling conditions, will be indicated in the test substance data sheet to be completed by the Sponsor.

An analytical certificate will also be provided by the Sponsor.

2.1.2 Vehicle

. **Denomination:** 0.5% methylcellulose

. **Batch No.:** will be documented in the raw data and specified in the study report

2.2 Formulation procedure

The test substance will be formulated in the vehicle. Fresh formulation of the test substance will be made by the CIT Pharmacy on the morning of administration.

2.3 Confirmation of test substance identity

The confirmation of the test substance identity is the responsibility of the Sponsor.

3. TEST SYSTEM

3.1 Animals

Species, strain: Sprague-Dawley rat ICO : OFA - SD. (IOPS Caw).

Reason for this choice: the rat is a rodent species generally accepted by regulatory authorities for this type of study.

Breeder: Iffa Crédo, 69210 L'Arbresle, France.

Number: two groups of ten animals (five males and five females each).

Age/weight: on the day of treatment, the animals will be at the most 6 weeks old, weighing 120 to 200 g and within a range not exceeding $\pm 20\%$ of the mean body weight of each sex.

Acclimatization: at least 5 days before the beginning of the study.

Allocation and identification of the animals: animals of each sex will be randomly assigned to the treatment groups according to the body weight recorded on day 1. Animals will be individually identified by earmarks or earnotches.

3.2 Environmental conditions

During the acclimatization period and during the main test, the animal room conditions will be set as follows:

- . temperature : $21 \pm 2^{\circ}\text{C}$
- . relative humidity : 30 to 70%
- . light/dark cycle : 12 h/12 h (7:00 - 19:00)
- . ventilation : approximately 12 cycles/hour of filtered, non-recycled air.

The temperature and relative humidity are under continuous control and recording. The records are checked daily and retained. In addition to these daily checks, the housing conditions and corresponding instrumentation and equipment are verified and calibrated at regular intervals.

The animals will be housed in polycarbonate cages with stainless steel lid (48 cm x 27 cm x 20 cm). Each cage will contain one to seven animals of the same sex during the acclimatization period and five rats of the same sex and group during the treatment period. Each cage will contain dust free sawdust (SICSA, 94142 Alfortville, France).

Bacteriological and chemical analyses of the sawdust, including the detection of possible contaminants (pesticides, heavy metals), are performed periodically by external laboratories.

The results of these analyses are archived at CIT.

3.3 Food and water

All animals will have free access to A04 C pelleted diet (UAR, 91360 Villemoisson-sur-Orge, France) and tap water (filtered using a 0.22 micron filter) contained in bottles, except as noted in § 4. "Treatment".

Each batch of food is analysed (composition and contaminants) by the supplier.

Bacteriological and chemical analyses of diet and water, including the detection of possible contaminants (pesticides, heavy metals and nitrosamines), are performed regularly by external laboratories.

The results of these analyses are archived at CIT.

No contaminants are known to be present in the diet, drinking water or bedding material at levels that may be expected to interfere with or prejudice the outcome of the study.

4. TREATMENT

4.1 Fasting of the animals

The animals will be fasted during the night before treatment, but they will have free access to water.

Food will be given back approximately 4 hours after administration of the vehicle or test substance.

4.2 Study design

The study design will be as follows:

Groups	Number of animals	Treatment	Dose-volume (ml/kg)	Dose-level (mg/kg)
1	5 males and 5 females	vehicle	10	0
2	5 males and 5 females	test substance	10	2000

4.3 Administration of the test materials

The oral route is selected since it is a possible route of exposure in humans.

The test substance formulation will be administered once to the animals of the treated group 2, under a volume of 10 ml/kg, using a glass or a plastic syringe fitted with a metal gavage tube.

The quantity administered to each animal will be adjusted according to the body weight recorded on the day of dosing.

The vehicle will be administered to the animals of the control group 1 under the same experimental conditions.

5. CLINICAL EXAMINATIONS

5.1 Clinical signs

The animals will be observed frequently during the hours following treatment and then at least once a day for a minimum period of 14 days. If necessary, the observation period will be prolonged.

5.2 Morbidity and mortality

Animals will be checked frequently during the hours following treatment for mortality or signs of morbidity, then at least twice a day thereafter.

Any animal showing signs of poor clinical condition, especially if death appears imminent, will be humanely killed (see § 6.1 Sacrifice).

5.3 Body weight

Body weight will be recorded on the day of treatment and then on days 5, 8 and 15 for the surviving animals. If the observation period is prolonged, body weight will also be recorded on the last day of the study. Individual weights of animals found dead during the study will be measured at necropsy if no signs of "cannibalism" is observed and when survival exceeds 24 hours.

6. PATHOLOGY

6.1 Sacrifice

On completion of the observation period, all surviving animals will be killed by carbon dioxide asphyxiation.

Throughout the study, any moribund animals will be killed in the same way.

6.2 Macroscopic examination

A macroscopic examination will be performed on all animals, including any that die during the study or are killed prematurely. After opening the thoracic and abdominal cavities, a macroscopic examination of the main organs (digestive tract, heart, kidneys, liver, lungs, pancreas, spleen and any other organs with obvious abnormalities) will be performed.

Any gross observations will be recorded individually.

Any organs showing a macroscopic lesion will be sampled and preserved in 10% buffered formalin.

6.3 Microscopic examination

No microscopic examination will be performed, in the first instance.

Organs showing a macroscopic abnormality will be preserved in fixative and subsequently processed and examined if requested by the Study Monitor.

7. PROCEDURES

The procedures used during the study will be those documented in the relevant CIT procedures manual.

8. AMENDMENTS TO THE PROTOCOL

If necessary, amendments to the protocol will be made after agreement between the Study Director and the Study Monitor.

9. REPORTING

The Study Director will contact the Study Monitor when necessary.

The final report in English, will contain all data collected throughout the study.

Number of copies of the final report: 3 (2 + 1 unbound) ...(1)...

Proposed issue of the draft report: 5 weeks after completion of the final necropsy.

10. QUALITY ASSURANCE UNIT

The study will be subjected to Quality Assurance monitoring in order to ensure compliance with GLP, specifically:

- (i) The study protocol will be checked for compliance with GLP requirements.
- (ii) Inspections will be carried out in order to ensure that the conduct of the study complies with Standard Operating Procedures and with the study protocol.
- (iii) Data audit will be undertaken to ensure the reliability and integrity of the study data.
- (iv) The study report will be reviewed by the Quality Assurance Unit in order to ensure that the report faithfully reflects the data generated during the study and the study findings.

The dates on which the findings of critical inspections and reviews are reported to the Study Director and CIT Management will be specified in the study report.

11. ARCHIVING

The study documentation and specimens generated during the course of the study will be archived at CIT, 27005 Miserey, Evreux, France, for 5 years after the end of the *in vivo* phase of the study.

The archived study materials will include:

- . protocol and possible amendments,
- . raw data,
- . correspondence,
- . final report and possible amendments,
- . possible histological specimens:
 - tissues in preservative
 - blocks
 - slides.

On completion of this period, the archived study materials will be returned to the Sponsor, or may be archived at CIT for a further period (at additional cost).

In addition, raw data not specific to the study including, but not limited to, certificates of analyses of food, water and bedding (if applicable) and records of environmental data and equipment calibration will also be archived at CIT and retained at least 30 years.

(1) Except for special request made by the Sponsor

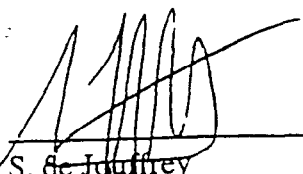
12. PROPOSED TIME SCHEDULE


First day of treatment: 18 March 1999

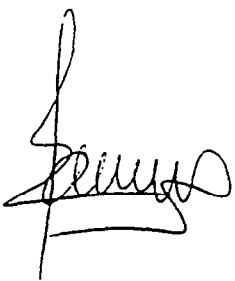
End of the observation period: 1 April 1999

In the case of modification, the dates of the study will be documented in the raw data and specified in the study report.

Protocol approved by:


S. de Jouffrey
CIT Scientific Management
Date: 23 FEB. 1999


J.C. Voirin
Study Monitor
Date: 1 MARS 1999


X. Manciaux
CIT Study Director
Date: 23 FEB. 1999

PRE MARKET NOTIFICATION

Extract of *Padina Pavonica* (EPP)

1. The name and address of the manufacturer of the new dietary ingredient:

Institute of Benthique Algae Limited
Unite F 24 Mosta Technopark
Valletta Road
Mosta MST 09
Malta

The name and address of the importer of the new dietary ingredient:

ExtractsPlus, Incorporated
3275 Corporate View Drive
Vista, CA 92083

The name and address of the encapsulator into dietary supplement:

SSI
5800 Newton Drive
Carlsbad, CA 92008

Distributor of the dietary supplement containing new dietary ingredient:

Perfect Equation
3275 Corporate View Drive
Vista, CA 92083

Advanced Nutratceutical Concepts
16 Sunnyview Drive
Phoenix, MD 21131

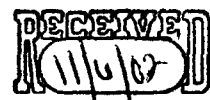
2. Name of the new dietary ingredient

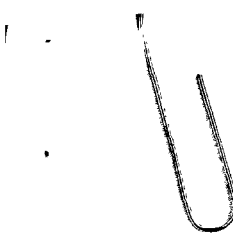
The name of the new dietary ingredient is EPP, an extract of the algae *Padina pavonica*.

3. Description

The description of the new dietary ingredient is as follows: EPP is a natural marine extract from the *Padina pavonica* brown algae; a member of the *Pheophyceae* genus. EPP is an off-white, odorless, fine powder that will be presented for use as a hard gel capsule.

4. Level of the new dietary ingredient in the dietary supplement and conditions and range of use on labeling:





Each hard-gel capsule will contain 200 mg of dry EPP. Adults should take 1 capsule daily orally.

5. Safety:

Local divers handpick the algae throughout the year and deliver the plant to a dedicated laboratory on the Island of Malta. The dry Padina is active but activity varies with harvest site, season, depth, water temperature, light, and currents. I.B.A. applies its proprietary extraction process using strict guidelines to assure the safety and efficacy of the product. After extraction, testing by biological titration ensures the efficacy of the final product. Scientists measure calcium fixation by osteoblasts for each batch to ensure consistency and maximum efficacy among batches.

Following European law CEE/67/548 EPP was tested for safety on rats and has been found to be non-toxic and safe for ingestions. See the Chrysalis Report #944/007 of December 30, 1997 (attached as Exhibit A). EPP is non-toxic or mutagenic per Ames II Assay. See the Xenometrix Report #BIO-1097 of October, 1997 (attached as Exhibit B). Toxicity studies in animals show dosages of > 2000 mg/kg without toxicity (attached as Exhibits C and D).

In Asia, Padina pavonica is used as a food according to the United Nations Organization for Nutrition and Agriculture (attached as Exhibit E). In addition, for more than a generation, people in Mediterranean countries have eaten these algae.

Based upon the information summarized above and the attached Exhibits, we have concluded that the dietary supplement containing this new dietary ingredient is reasonably expected to be safe.



(M) Ltd.

Institute of Benthique Algae

0648 '03 FEB 25 P1:54

Unit F24, Mosta Technopark, Mosta MST 09, MALTA. Tel: (00356) 438458. Fax: (00356) 419778
Reg. No. 1444 7712 Co. Reg. No. C.70704 MALTA

21st October 2002**To whom it may concern:**

The attached studies use a variety of names and designations for the test materials. These names:

APO G, ADS 11, HPS 3, Padinol Solide ,EPP

We confirm that each of these test materials is a native extract of *Padina pavonica* (EPP) and that these materials were produced using the same process as that used for the production of EPP.

Gilles Gutierrez Ph.D. (Pharmacology)
President

A handwritten signature in black ink, appearing to be 'Gutierrez', written over a white background.

Directors: C. M. Saliba (Managing), G. Gutierrez, J. Pierresalles